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Diagnostics chapter

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Introduction

Over the last two decades the heady expectations of a genomic revolution in biomedicine have been accompanied by much debate about whether the regulatory regimes that govern diagnostic tests are sufficiently robust to cope with the challenges that this brave new era might present. A persistent concern has been the pace of innovation and the paucity of the evidence base to inform clinical adoption of new genetic tests. As one diagnostics industry executive described the problem in 2003 (Winn-Deen 2003):

> [There has been] a noticeable lack of consensus within the genetics community about exactly when a test for a new marker was sufficiently validated for it to enter into clinical service. Some labs rushed to provide testing after the first publication, while others waited until the result had been replicated in multiple studies or multiple ethnic groups.

With the growing use of companion diagnostics and multi-marker prognostic signatures in oncology, and an increasing number of firms marketing pharmacogenetic tests or polygenic risk assessment for common, complex diseases, this issue is no longer confined to the field of rare disease genetics. Although the development of next-generation sequencing and non-invasive sampling techniques has sparked new concerns about the pace of DNA-based diagnostic innovation, the emerging fields of metabolomics and proteomics are broadening our definition of personalised medicine and further complicating the regulatory challenges. Given the pace of technological change, the field of molecular diagnostics continues to face significant challenges in validating the technical performance of new platform technologies, and in evaluating the clinical significance of new biomarkers.

Focusing primarily on Europe and the USA, this chapter describes how the regulatory frameworks for diagnostic technologies are changing, in part as a response to technological advances in (and with likely significant consequences for) personalised medicine. The chapter will provide an overview of how policy deliberation about the regulation of genomic diagnostics has evolved over the last two decades, and sets this policy debate in the context of broader concerns about the scientific rigour of diagnostic innovation. The chapter then describes policy developments in the statutory regulatory regimes that govern diagnostic tests as medical devices; the construction of a new regulatory regime for pharmacogenomics; and the growing role of health technology assessment as a gatekeeping mechanism.

A key argument advanced in this chapter is that it would be a mistake to simply characterise personalised medicine as another field where scientific advance has outstripped public policy. In practice, two decades of ELSI research, policy reports and public debate have anticipated the potential challenges of a scientific field that has advanced into the clinic at a scale and pace considerably less dramatic than many expected. If there is a lag, it is in moving from policy

deliberation to policy implementation, and even in this respect the record is mixed.

A second key argument is the need to move beyond an approach that focuses solely on the challenges of the cutting-edge of technological change, a bias inherent in ELSI research funding. Concerns about diagnostic innovation are not restricted to molecular diagnostics and personalised medicine - a 2015 report from the National Academies of Science (NAS) suggested that in the USA, diagnostic errors are implicated in approximately 10 percent of patient deaths, and 6-17 percent of hospital adverse events. Amongst its many recommendations, the report emphasised the need for more robust evaluation of new diagnostic tests before they enter clinical practice (The National Academies of Sciences, Engineering, and Medicine 2015). A 2015 report from the US Food and Drug Administration (FDA) similarly highlighted the risks to patients arising from poorly validated diagnostics (Food and Drug Administration 2015).

Finally, this chapter advances the argument that, in comparison with the burgeoning literature devoted to pharmaceutical regulation, the regulation of diagnostic tests has been a relatively neglected subject for social scientists, historians and legal scholars interested in biomedicine. ELSI scholarship has done little to rectify this imbalance; there has been far more research on topics such as biobank governance than downstream commercialisation of genomic diagnostics. In this chapter I will offer some suggestions for future research that might begin to fill this gap.

An evolving policy debate

Regulatory policy and ELSI scholarship has evolved over more than two decades, repeatedly shifting focus in response to technological innovations (such as next-generation sequencing), the emergence of new diagnostic modalities (such as companion diagnostics), and changes in the way that tests are delivered (such as direct-to-consumer (DTC) services). Alongside these dynamics, which we might characterise as endogenous to the field of genomics, are a broader set of exogenous factors that have shaped policy. Consider, for instance, the field of pharmacogenomics, a term used to describe the application of genomic science in drug discovery and development, and the clinical use of pharmacogenetic tests to guide drug selection and dosage decisions based on information about how an individual's genetic make-up might influence drug metabolism. Here regulatory standards have developed through collaboration between regulatory agencies in the USA, Europe and Japan, reflecting the growing importance of transnational harmonisation in pharmaceutical regulation.

If one were to attempt a chronological sketch of the evolving policy debate, one might suggest that the earliest topic of debate was newborn screening for monogenic diseases (see for instance Nuffield Council on Bioethics 1993; National Research Council (U.S.). & Committee for the Study of Inborn Errors of Metabolism 1975). However, for a decade or so from the mid-1990s the topic attracting greatest attention was genetic risk prediction for common, complex

diseases (CCDs). The discovery of the link between the APOE gene and Alzheimer's in 1992 and the discovery of the BRCA 1/2 genes linked to breast and ovarian cancer in 1994/5 fuelled much debate about the clinical utility of genetic risk factors for common complex diseases (CCDs), the psycho-social consequences of genetic risk assessment, and the dangers of premature clinical adoption when data on the predictive value of risk markers was still evolving. A succession of policy reports highlighted concerns about predictive genetic tests (sometimes referred to as susceptibility tests). ELSI scholarship in this period was primarily concerned with mapping the different regulatory actors and their respective powers and functions, comparative analysis of regulatory regimes in different countries, and proposals for regulatory reform (Javitt & Hudson 2006; Martin & Frost 2003; Hogarth et al. 2007).

Given the very limited number of predictive genetic tests that were available in this period, and the limited scale of their diffusion into clinical practice, this phase of policy deliberation might be viewed as a timely example of anticipatory governance; an effort to ensure that public policy did not lag behind technological change. Yet, in 2007 when a new wave of direct-to-consumer (DTC) genomics firms like Navigenics and 23andme began offering polygenic susceptibility tests for a range of CCDs, , some ELSI scholars cautioned that regulatory action was still premature (Prainsack et al. 2008). DTC genomics subsequently became a popular topic for ELSI research, and concerns about DTC firms continue to frame much of the regulatory debate and, in the USA at least, have galvanised regulatory enforcement activity.

Moreover, by 2007 the attention of policymakers and regulatory agencies had diffused well beyond susceptibility testing. A wave of ELSI research and policy reports from around 2003 onwards had focused on pharmacogenomics (Hogarth et al. 2006; Hopkins et al. 2006; Melzer et al. 2003). Policymaking in this area was marked by a greater involvement of industry actors and a relatively minor role for the clinical genetics community (who were key actors in the debate about susceptibility testing). Other developments that have broadened the framing of the regulatory debate (but which this brief chapter lacks space to address), include the growing number of firms marketing proprietary multi-marker diagnostic signatures and the clinical application of two new technologies: next-generation sequencing and non-invasive prenatal testing.

Perhaps the most significant shift in framing might be very broadly characterised as a transition from 'innovation is too fast', to 'innovation is too slow'. This change was perhaps most clearly apparent in the USA, where it was linked to the deregulatory agenda of President Bush (Stewart 2002). In 2002 the new Bush administration disbanded the Secretary's Advisory Committee on Genetic Testing, a body which had focused its attention on regulatory reform, and replaced it with a new body: the Secretary's Advisory Committee on Genetics Health and Society, which

began its work by explicitly stating that it would not address regulatory issues and then produced a series of reports that were chiefly concerned with barriers to innovation, such as reimbursement (SACGHS 2006) and gene patenting (SACGHS 2010). Concerns about how weaknesses in the regulatory regime for diagnostics lead to the clinical adoption of tests with limited evidence of safety and effectiveness have not been supplanted (Hayes 2015) – indeed, even SACGHS produced an important report on the topic in 2008 during the dying days of the Bush administration (SACGHS 2008) - but they are now supplemented by concerns about how fundamental failings in the diagnostic R&D process have resulted in disappointing progress in translating biomarker discoveries into clinical diagnostics (Wagner & Srivastava 2012; Poste 2011). This change in framing, emerged in part from a growing consensus that major investments in genomic science have thus far had limited clinical impact (Evans et al. 2011; Green et al. 2011), but also from recognition that the limitations of the current diagnostic innovation process have a broader societal impact, in particular the opportunity costs of misdirected public and private funding in biomedical research and healthcare (Henry & Hayes 2012; Califf 2004).

A flawed system

Much diagnostic innovation has traditionally occurred at the interface of the clinic and the laboratory, in a "hidden innovation system" which is rarely subject to formal regulatory controls (Hopkins 2006). The field of clinical genetics has exemplified the dynamics of this innovation model, in which clinicians and researchers based in the public sector play the lead role in the discovery and development of new biomarkers and new diagnostic techniques, and industry plays a supporting and secondary role. This model involves often very diffuse networks of actors operating without a clear co-ordinating central node; there is no single sponsor of a new technology, in the way that a pharmaceutical firm is the sponsor for a new therapeutic molecule. Hopkins has characterised this innovation system as "hidden", both because it is often neglected in policy discourse, and because it has flown under the radar of formal oversight processes. Its diffuse and non-commercial character means that it generally evades both the statutory regulatory mechanisms that establish scientific standards for the safety and efficacy of medical devices by controlling market entry, and the soft law regulatory constraints of healthcare payors, who use Health Technology Assessment (HTA) to demand evidence of comparative clinical or cost effectiveness of new medical technologies.

In recent years, the hidden innovation model has been bolstered by enhanced funding for translational science programmes that encourage "novel forms of clinical research designed to extend genomics into the clinic" (Kohli-Laven et al. 2011). If much of the policy debate around genetic testing oversight sought to create a clearer delineation of research and clinical practice

(see for instance, the recommendations of the Task Force on Genetic Testing 1997), then arguably these recent developments have blurred the boundaries further. Such porous borders may provide valuable grist to the intellectual mill of STS scholars eager to map the heterogeneous networks of actors at work in this space, but from the perspective of public policy they serve only to heighten concern about a series of fundamental problems with diagnostic innovation, a field in which, critics suggest, researchers "have often ignored ... fundamental principles of the scientific process" (Hayes 2013). Advocates of what we might term *diagnostic reform* suggest that the failings in diagnostic R&D are multiple. Commonly cited problems include underpowered studies, various types of bias, insufficient research on clinical outcomes, over-fitting of data in retrospective analyses and a lack of prospective controlled studies (Feinstein 2002; Sox Harold C 1996). The porous boundary between research and clinical practice enables continued confusion over the appropriate scientific standards for diagnostic innovation.

Personalised medicine has not escaped these problems. For many years, research on the genetic epidemiology of CCDs was characterised by an overwhelming failure to replicate findings. A 2006 review by Ioannidis et al described the field as dominated by small, underpowered studies, often with flawed designs and selective reporting of positive results (Ioannidis et al. 2006; Morgan et al. 2007). However, from 2007 a new wave of large-scale Genome-Wide Association Studies (GWAS), often organised as transnational collaborations, overcame the problem of small sample size and began to produce robustly replicated findings, but this development simply pushed the evaluative challenge downstream, presenting new challenges in how to validate the clinical validity and utility of polygenic susceptibility testing (McCarthy et al. 2008).

Again, these problems reflect broader challenges for the cause of diagnostic reform, in particular the need for regulators to establish and enforce clear scientific standards. As a recent commentary has suggested, in the absence of clear standards, uncertainty prevails:

> ... manufacturers, laboratory professionals, researchers and regulators are equally confused on what studies to do or accept as evidence for the clinical performance and effectiveness of medical tests (Horvath et al. 2014).

The changing terrain

In terms of statutory regulation, notable developments are the introduction of new regulations for diagnostic devices in the European Union (EU) in 2017 and in Australia in 2010, and efforts by the US Food and Drug Administration to establish a new regulatory framework for laboratory-developed tests (LDTs). Beyond these statutory regulatory frameworks, the last decade has seen initiatives to improve the evaluation of genomic diagnostics, including

development of the ACCE evaluation framework (see table below) and the creation of evaluative bodies such as the UK Genetic Testing Network (Hogarth 2007). Broader diagnostic reform efforts have been promulgated by two interlinked communities: HTA and Evidence-Based Medicine (EBM), from which have emerged new standards such as the STARD framework for reporting diagnostic studies (Bossuyt et al. 2003). Such developments exemplify a broader process of regulatory expansion in the regimes governing healthcare technology adoption, in particular growing demand for evidence of comparative and cost-effectiveness by HTA agencies, and a greater role for clinical guidelines (Weisz et al. 2007; Timmermans & Berg 2010).

ACCE framework for test evaluation	
Analytic validity	accuracy of test identifying the biomarker
Clinical validity	relationship between the biomarker and clinical status
Clinical utility	likelihood that test will lead to an improved outcome
Ethical, legal and social implications	

Regulating diagnostic devices

In the United States, the FDA was granted the legal authority to evaluate the safety and effectiveness of medical devices by the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FDCA). According to the statutory definition, a medical device is deemed safe if the scientific evidence demonstrates "that the probable benefits to health … outweigh any probable risks" (US FDA: Code of Federal Regulations Title 21 § 860.7(d)(1)). Effectiveness is demonstrated when scientific evidence shows that "in a significant portion of the target population, the use of the device … will provide clinically significant results" ((US FDA: Code of Federal Regulations Title 21 § 860.7(e)(1)). How are these terms operationalised in the case of diagnostic devices? The FDA generally states that it is interested in two performance criteria: analytic validity and clinical validity. However, the term "clinically significant results" is sufficiently ambiguous to merit closer attention. Social scientists could usefully investigate how this term has been operationalised in regulatory guidance documents and in regulatory decision-making, for instance, has the threshold for approval changed over time or does it vary significantly for different types of test?

In the European Union, the IVD Directive, which came into force in 2003, is commonly understood as allowing manufacturers to validate their tests based solely on analytic performance although Hogarth and Melzer (2007) have disputed this interpretation. Such interpretive disputes notwithstanding, the new EU regulation, which will come into force in 2017, places far greater emphasis on the need for manufacturers to provide data on the clinical

performance of diagnostic devices. Furthermore, a new risk classification system will ensure that a far greater proportion of diagnostic tests will be subject to regulatory scrutiny before market entry, including genetic tests, all cancer tests (the disease area where personalised medicine has advanced furthest) and all companion diagnostics. Specific provisions make explicit that the regulation will cover predictive genetic tests and DTC tests sold via the internet, two areas of ambiguity in the 2003 Directive. Despite a strengthening of regulatory controls, EU policymakers have been keen to present their approach as more flexible and less onerous than the USA's. Another area for future research would be to examine evidence of 'device lag', i.e. slower market entry in USA than EU. A more in-depth case study approach could examine which of the respective regulatory approaches offers the greatest protection against unsafe or ineffective medical devices.

Laboratory-Developed Tests

In the USA, the FDA's authority over genetic tests has been the subject of high-level policy reports, Congressional hearings and a number of different draft legislative proposals. The key regulatory loophole is not specific to genomics, but relates to what are now generally termed laboratory-developed tests (LDTs), i.e. a diagnostic test "that is intended for clinical use and designed, manufactured and used within a single laboratory" (Food and Drug Administration 2014). The regulatory status of LDTs was first highlighted by the 1997 US Task Force on Genetic Testing (Hogarth et al. 2007). Since about 2003 the FDA has asserted its regulatory authority over LDTs on an ad hoc basis, but there has been resistance to proposals for a more systematic approach. Critics of FDA's move to regulate LDTs argue that such tests are already adequately regulated under the statute which governs clinical laboratories. However, FDA has twice been given direction from Congress to address at least some portions of the LDT sector, and in the last decade two policy reports from government advisory committees have recommended FDA regulate LDTs, arguing that the agency has the necessary legal authority, scientific expertise and regulatory experience to extend its oversight to this sector of the diagnostics market (SACGT 2000; SACGHS 2008).

FDA's earliest effort to progress this issue was stymied by Bush administration political appointments to the agency in 2001. Limited progress was made under President Obama, in the shape of two draft guidances and continued ad hoc regulatory interventions against specific firms, but the failure to finalise guidance setting out a new framework is testament to the conservatism of the New Democrat politics of the Obama administration. Although draft legislation continues to be discussed in Congress, the prospects for progress under President Trump seem remote.

Other jurisdictions have begun to address the regulatory status of LDTs. Furthest advanced is

Australia, where a new regulatory framework for IVDs was introduced in 2010, in part specifically to address oversight of the LDT sector by the Therapeutic Goods Administration (TGA). For low- and moderate-risk tests, laboratories must be ISO accredited, must register with the TGA and notify the agency about the tests they make. Test validation must meet TGA-endorsed standards, but will be carried out by the National Association of Testing Authorities (NATA) and the National Pathology Accreditation Advisory Council (NPAAC), the bodies responsible for assuring laboratory performance in Australia. Only high-risk tests will be subject to the same standards and processes as apply to test kits. This is an example of what regulatory theorists term 'responsive regulation': it strikes a balance between on the one hand relying wholly on either 'command-and-control' powers exercised by a central agency, or on the other hand focusing purely on mechanisms of self-regulation.

Although the precise details are somewhat different, the Obama administration-era draft FDA guidance had marked similarities: a risk-based approach with a variety of exemptions, the use of registries for tests exempt from full oversight, and a role for third-parties in the governance process. The draft new EU IVD regulation retains a distinction between devices produced in health institutions (which are mainly exempt) and what it terms "devices used in the context of a commercial activity to provide a diagnostic or therapeutic services" (Para 19 of Recital), which are not exempt. Although the regulation contains ambiguous wording and arguably contradictory clauses, and is likely to require additional clarifying guidance, even for health institutions, the new regulation will move closer to the TGA model and FDA's proposed model, with regard to high-risk LDTs produced in health institutions.

These areas of convergence suggest a policy space where a degree of transnational policy learning may be underway. An immediate priority for future research would be to investigate how the new Australian regulations are working in practice, a topic likely to be of interest in multiple jurisdictions that have yet to address this regulatory issue, for instance Canada, or where policy is still in a state of flux (as in the United States and the European Union).

Pharmacogenomics

Pharmacogenomics is the use of genomic science to study human variability in drug response. Proponents of pharmacogenomics suggest that it will lead to a fundamental transformation both in pharmaceutical R&D and in clinical practice, but uncertainty about the regulatory standards and processes for this emergent technological paradigm has been widely cited as an obstacle to more widespread and rapid adoption. However, in 2004 the FDA and the EMA each published reports suggesting that genomics would be a key component in a new scientific toolkit for drug development that would solve the pharmaceutical industry's longstanding productivity crisis; enable cheaper and faster drug development; and provide safer and more effective drugs

(European Medicines Agency 2005; Food and Drug Administration 2004). Both agencies asserted a central role for themselves in the translation of genomics from bench to bedside. Pharmacogenomics thus presents an ideal case study of the role of regulators in the co-production of new biomedical technologies. Since 2004 a process of organizational restructuring, standard-setting and regulatory decision-making has constructed a new transnational regulatory regime for pharmacogenomics through an iterative process of regulatory experiment enacted by a network encompassing regulatory agencies in the USA, EU and Japan in conjunction with academic scientists and industry (Hogarth 2012). This process has been marked by the creation of new socio-technical spaces in the regulatory regimes for pharmaceuticals – a pre-regulatory space for the sharing of data outside the regulatory decision-making process and a pre-competitive space for the sharing of data between firms. It was marked also by the expansion of a transnational regulatory space for sharing data and setting standards across jurisdictional boundaries. The construction of this new regulatory paradigm was both driven by and reinforced the existing trend towards transnational governance in pharmaceutical regulation, and in particular it bolstered the growing authority of EMA as the *de facto* regulator for novel biomedical technologies in Europe.

Another dynamic worthy of note is how the 2004 reports from FDA and EMA repositioned the agencies as enablers of innovation, the subsequent close interaction with industry in policy development and the repeated emphasis on faster and cheaper drug development as a key goal (Hogarth 2015). The construction of a regulatory regime for pharmacogenomics has thus been consistent with what Davis and Abraham term the era of *neoliberal corporate bias* in pharmaceutical regulation (Davis & Abraham 2013).

HTA for diagnostics

In the past, the decision on whether or how to use a test was a question for the clinical judgement of individual physicians, however, increasingly these decisions are made formally by healthcare funding or reimbursement systems, or health service provider organisations. The process of approval or recommendation is generally based on a review of the available evidence, a practice generally known as health technology assessment (HTA). One recent study suggests that new molecular diagnostics face heightened scrutiny by HTA agencies in the USA compared with more traditional diagnostic tests (Trosman et al. 2011), and the last decade has seen new initiatives to advance evidence-based evaluation of diagnostics, such as the diagnostics assessment programme established by the UK's National Institute for Health and Care Excellence, and the EGAPP process supported by the US Centers for Disease Control.

The growing importance of HTA for diagnostic innovation is illustrated by the Roche Amplichip, which in 2004 became the first pharmacogenetic microarray test to gain FDA approval. In the

USA it was taken up by LabCorp, the country's second largest reference lab and was therefore widely available. However, a succession of negative HTA reports found insufficient evidence of clinical utility to support the use of the Amplichip to guide drug treatment (Blue Cross Blue Shield Technology 2004). This example illustrates the profound temporal and spatial bifurcation in the operation of power within the diagnostic regulatory regime. In the premarket space regulatory power accords with a traditional model of command-and-control regulation in which the sovereignty of the regulatory agency over the regulated industry is paramount, but in the postmarket space power is much more diffuse: not only is the balance of power between regulator and industry more equal but the role of gatekeeper is shared amongst multiple actors (Hogarth & Martin 2015). The changing power dynamics within this multi-level regulatory regime are a further topic for future research, for instance is the trend towards convergence or divergence in the standards applied by regulatory agencies like FDA and HTA bodies?

Conclusion

This chapter began by suggesting that of the regulation of diagnostic technologies has been a neglected research topic and in conclusion I will identify some ways forward. Concerns about the scale and pace of innovation in genomics are indicative of an unresolved tension between personalised medicine and evidence-based medicine. Examining the interactions and overlaps between the two distinct but related epistemic communities would be one fruitful approach for future research.

Whether flying under the banner of ELSI or RRI, researchers who believe that anticipatory governance mechanisms can play a useful role in steering biomedical innovation need a degree of reflexivity, and historical reflection on developments in this field may prove helpful. Well-characterised regulatory issues, highlighted over decades in a succession of policy reports produced in multiple jurisdictions have impelled administrative action and legislative reform but have yet to find final resolution. We might usefully interrogate the translational space between policy recommendation and policy implementation in search of lessons for the future.

There are strong drivers in ELSI funding mechanisms and in the intellectual orientation of STS scholarship for a focus on emergent technologies. The recent STS turn against innovation and towards maintenance (Russell and Vinsel 2016) offers hope for greater attention to the realm of everyday, established technologies and suggests an important direction for future scholarship on the regulation of diagnostics. The cutting-edge of personalised medicine will remain an important field of inquiry but future research should also investigate the dynamics of standard-setting and regulatory approval for mundane, but pervasive diagnostic technologies such as glucose meters.

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